

AD-A091 476

ARMY MEDICAL RESEARCH INST OF INFECTIOUS DISEASES FR--ETC F/G 6/5  
IRON NUTRITION, IMMUNITY AND INFECTION; (U)  
OCT 80 W R BEISEL

UNCLASSIFIED

NL

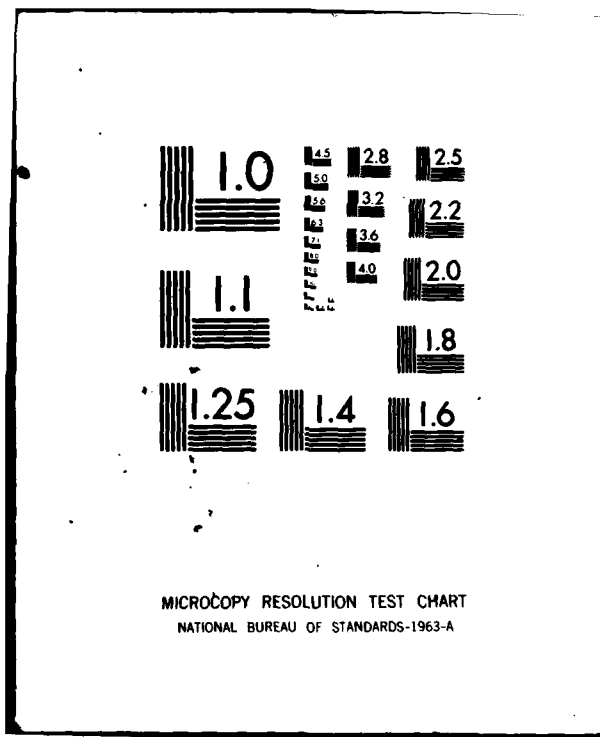
END

DATE

FORMED

51-1-

DTIC



UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
	AD-A091476	
4. TITLE (and Subtitle)		5. TYPE OF REPORT & PERIOD COVERED
Iron Nutrition, Immunity and Infection		
7. AUTHOR(s)		6. PERFORMING ORG. REPORT NUMBER
William R. Beisel M.D.		
9. PERFORMING ORGANIZATION NAME AND ADDRESS		8. CONTRACT OR GRANT NUMBER(s)
US Army Medical Research Institute of Infectious Diseases Fort Detrick, Frederick, Maryland 21701		(12) 19
11. CONTROLLING OFFICE NAME AND ADDRESS		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
US Army Medical Research and Development Command, Office of The Surgeon General Department of the Army, Washington, D.C. 20314		S10-AQ-175
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		12. REPORT DATE
LEVEL		28 October 1980
		13. NUMBER OF PAGES
		16
		15. SECURITY CLASS. (of this report)
		UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report)		
Approved for public release; distribution unlimited		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
Information regarding reprints are not available at this time This is an invited article for Resident and Staff Physician		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
Infectious Disease                      Anemia Iron    Protein-energy Malnutrition Transferrin Lactoferrin Iron-binding Capacity		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		
During infection, physiological mechanisms withhold iron from invading microorganisms by sequestering it in tissue stores. These mechanisms increase the concentration of unsaturated transferrin in plasma by reducing plasma iron values. In contrast to the need for iron administration in patients with iron-deficiency, therapeutic iron is of no benefit and may be harmful if given during infection. In patients with coexisting protein-energy malnutrition and iron deficiency, iron therapy may be associated with the reemergence of a latent infection.		

DD FORM 1 JAN 73 1473

EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

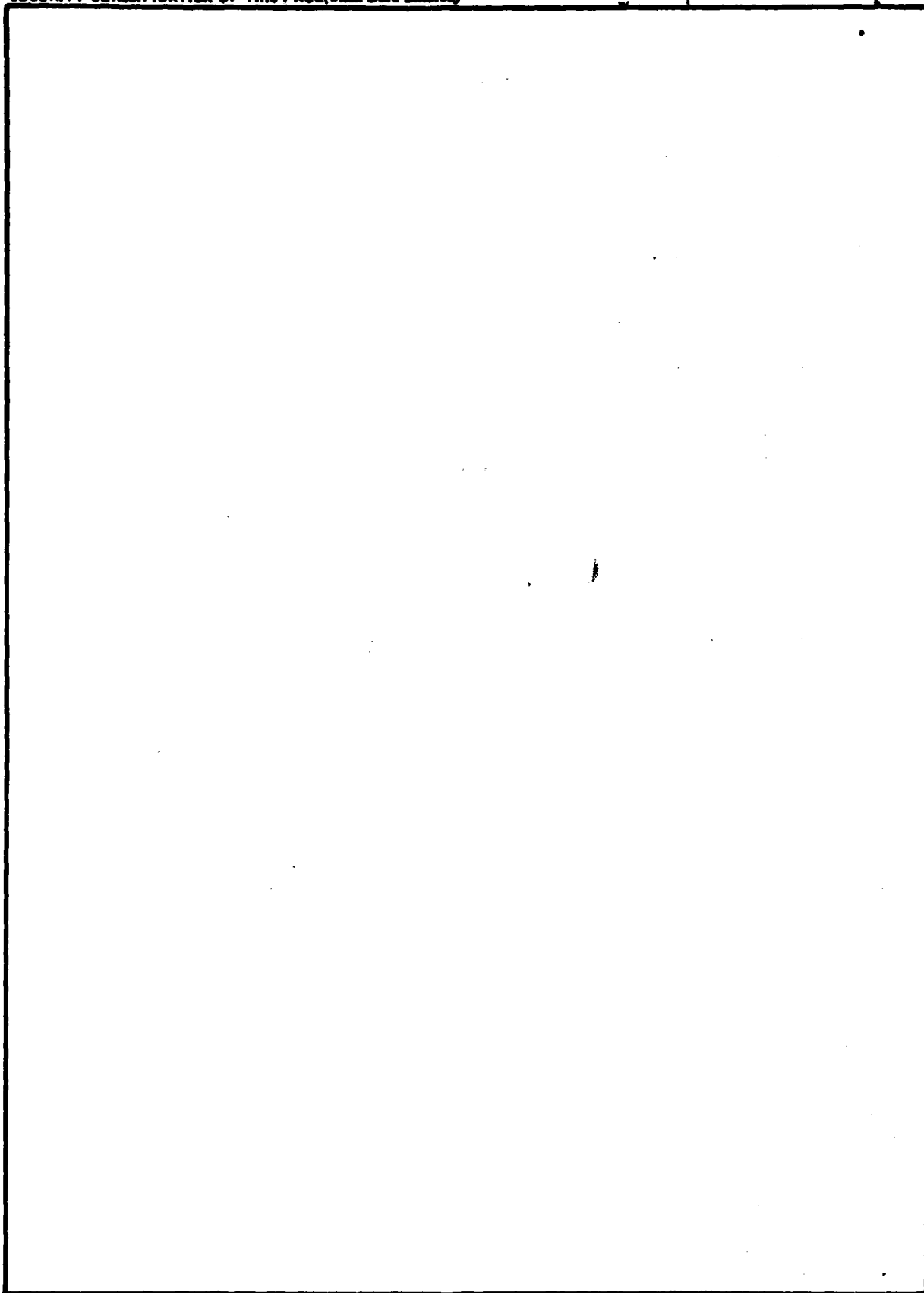
405039

AD A091476

DTIC  
ELECT  
NOV 21 1980

REF ID: A091476

SECURITY CLASSIFICATION OF THIS PAGE(When Data Entered)



SECURITY CLASSIFICATION OF THIS PAGE(When Data Entered)

Iron Nutrition, Immunity and Infection

By

William R. Beisel, M.D., F.A.C.P.

Deputy for Science

US Army Medical Research Institute of Infectious Diseases

Fort Detrick, Frederick, Maryland 21701

An invited article for

Resident and Staff Physician

The views of the author do not purport to reflect the positions  
of the Department of the Army or the Department of Defense

28 October 1980

Approved for public release; distribution unlimited

FILE COPY

80 11 12 127

**Iron Nutrition, Immunity and Infection**

**By**

**William R. Beisel, M.D., F.A.C.P.**

**Deputy for Science**

**US Army Medical Research Institute of Infectious Diseases**

**Fort Detrick, Frederick, Maryland 21701**

**An invited article for**

**Resident and Staff Physician**

**The views of the author do not purport to reflect the positions  
of the Department of the Army or the Department of Defense**

### Abstract

During infection, physiological mechanisms withhold iron from invading microorganisms by sequestering it in tissue stores. These mechanisms increase the concentration of unsaturated transferrin in plasma by reducing plasma iron values. In contrast to the need for iron administration in patients with iron-deficiency, therapeutic iron is of no benefit and may be harmful if given during infection. In patients with coexisting protein-energy malnutrition and iron deficiency, iron therapy may be associated with the reemergence of a latent infection.

Accession For	
NTIS GRA&I	<input checked="checked" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	
By _____	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A	

Iron is an essential micronutrient for almost all forms of life. The human body possesses elaborate protective mechanisms which serve in well nourished persons to regulate the content of iron in body fluids. Mechanisms also exist to initiate an abrupt redistribution of iron within the body as a defensive measure. These latter mechanisms are activated during episodes of infectious disease, and by increasing the concentration of unsaturated transferrin in plasma, they apparently help to minimize the availability of iron for many varieties of invading microorganisms which need iron to permit growth and replication (1).

The iron-binding capacity of plasma is provided chiefly by transferrin and to a much smaller degree by lactoferrin. The association constant of transferrin for iron is above  $10^{30}$ , and under normal circumstances only to to 30% of the plasma transferrin is saturated. Thus, at equilibrium, the amount of free ionic iron in plasma is approximately  $6 \times 10^{-15}$  M, an amount at least  $10^8$ -fold lower than that required for the growth of most bacteria. To capture iron from the host, microorganisms must synthesize their own iron-sequestering compounds to compete with transferrin (2, 3).

Studies in experimental infections (4-6) show that the administration of exogenous iron in transferrin-saturating doses can block the iron-lowering defensive mechanisms of laboratory animals and thereby permit an overwhelming proliferation of pathogenic microorganisms. Similarly, several clinical reports (7, 8) suggest that the administration of iron as a nutritional



component of refeeding programs for starved children may stimulate the reemergence of clinically active infections such as malaria, brucellosis, or tuberculosis.

#### Iron Deficiency

Observations such as these raise potential questions concerning the safety of iron therapy regimens employed for the correction of iron deficiency anemia in malnourished patients. Iron deficiency continues to be one of the most common nutritional problems in all lands. Even in industrialized societies, iron losses in women are of widespread and continuing importance, leading at times to the production of a single nutrient deficiency state during the menstrual years. Varying degrees of iron deficiency also accompany most instances of protein-energy malnutrition in children.

A lack of adequate body stores of iron leads not only to iron-deficiency anemia but also to anatomical and functional changes in the lymphocytic and phagocytic cells which are of vital importance for maintaining normal immunocompetence and other aspects of host defense. Lymphocyte subpopulations may be reduced in iron-deficient children, and the propensity of peripheral blood lymphocytes to respond to mitogens or antigens may be impaired during in vitro tests (9). Iron-deficient patients may also fail to develop a positive delayed dermal hypersensitivity response to ubiquitous skin-test antigens.

Iron deficiency has been found to produce important decrements in the functional activity of phagocytic cells, especially in their ability to kill ingested bacteria. Iron deficiency impairs the synthesis of nucleic acids in dividing cells and reduces the activity of iron-containing enzymes, including those necessary for the production of activated bactericidal oxygen radicles (1, 4, 9). For these reasons, a deficiency of iron can increase the susceptibility of a patient to infection.

#### Approaches to Therapy

Therapeutic uncertainties concerning the need for administering exogenous iron should be approached in a rational manner. Sound diagnostic findings must be established in order to determine if a patient needs iron, or if the administration of iron is likely to lead to an increased possibility of an infectious complication. Therapeutic judgements should be based upon three key factors: 1) an understanding of infection-induced changes in body iron metabolism; 2) measurements of the concentration of unsaturated iron-binding proteins in plasma; and 3) estimates of the body content of iron in a given patient. An evaluation of these factors will allow the physician to determine if a patient needs iron therapy or if such therapy is unnecessary, and, importantly, if the administration of iron will carry a potential risk for increasing the likelihood of infection.

### Iron and Infection

An abrupt redistribution in the localization of iron within the body occurs as one of the generalized host defensive mechanisms, and is stimulated by pathogenic processes that activate phagocytic cells. This redistribution of body iron is initiated early in the course of an infectious process. Iron redistribution is characterized by an abrupt increase in the uptake of plasma iron by certain body cells. Iron which is normally bound to plasma transport proteins moves in increased amounts into the cells of the liver as well as into reticuloendothelial cells of the marrow and spleen where the iron becomes sequestered in one of two storage forms, i.e., as granules of hemosiderin iron or as ferritin (1).

As shown in Figure 1, the infection-induced redistribution of iron causes the concentration of iron in plasma to decline markedly. The onset of hypoferremia is determined by the kind of infection as well as by the length of its incubation period. Hypoferremia generally begins a day or two before the onset of fever and symptoms and then persists into the convalescent period. This phenomenon is most prominent in bacterial infections, especially pyogenic ones, but it occurs in viral infections as well. On the other hand, during the second and third week of viral hepatitis, plasma iron increases to above-normal values, possibly because the damaged liver cells are unable to take up or retain the iron (1).

The abrupt redistribution of body iron is stimulated by the release of an endogenous mediating factor from white blood cells which are activated by phagocytosis of particulate matter or stimulated by soluble factors such as antigen-antibody complexes. Following its release, this leukocytic factor, which is akin to endogenous pyrogen, appears to act directly on the liver and marrow. When tested in bioassay animals, this factor initiates hypoferremia within 3 to 4 hours after its injection (1).

The mechanisms leading to the sequestration of iron within the liver during infection are sufficiently strong that the stored iron is held physiologically in a status of reduced availability (1, 10). This sequestration of iron may contribute to the "anemia of infection" if the disease process is not eliminated. Because this form of anemia is microcytic and occurs in the presence of low plasma iron values, it is often mistaken for iron deficiency anemia (10). If iron is administered therapeutically in an attempt to correct the "anemia of infection" it will fail to do so. Rather, the administered iron will also become sequestered in cellular storage sites (1, 10).

#### Iron Binding Proteins

The abrupt decline in plasma iron concentrations during an infection results in a reciprocal increase in the concentration of unsaturated transferrin. Transferrin concentrations can be measured directly or estimated indirectly by measuring the

iron-binding capacity of plasma. The infection-induced decline in plasma iron, sometimes to virtually nondetectable quantities, serves the host as a nonspecific defensive mechanisms by increasing unbound transferrin to maximal values.

Transferrin and other iron-binding proteins such as lactoferrin have been identified as major antimicrobial factors which are present in plasma, tissue fluids, or milk. Their antimicrobial activity resides in their extremely high binding affinity for iron. This affinity is sufficiently high that the binding proteins can take up the iron in biological fluids and thereby deny its availability to any microorganisms that are present. However, if the capacity of transferrin or lactoferrin for binding iron becomes saturated, these proteins lose their antimicrobial effects (2-6).

In addition to the protective roles of unsaturated transferrin in plasma and secreted lactoferrin in milk, lactoferrin also plays an antimicrobial role in localized inflammatory reactions. Lactoferrin is contained within specific (secondary) cytoplasmic granules of neutrophils and can be detected immunologically after the granules have been lysed. Trace amounts of lactoferrin are normally present in serum (about 0.3 to 0.4 mg per 100 ml) and other body fluids. The ability of lactoferrin to carry ferric iron is roughly equivalent to that of transferrin (1). Lactoferrin is one of the proteins secreted by leukocytes when they are activated by phagocytosis. The release of this antimicrobial

protein at sites of a localized infection or inflammatory reaction helps to deny iron to any organisms that may be present.

In contrast to the abrupt decline in plasma iron, total transferrin values do not change appreciably during most infections, although a slight decline may become evident if an infection becomes subacute or chronic.

In the presence of severe iron-deficiency, plasma transferrin values respond by developing a marked increase, often to concentrations twice those of normal. On the other hand, during states of generalized malnutrition, especially those in which deficits of protein are a major factor, total plasma transferrin values decline. Transferrin may fall during severe generalized malnutrition to values only half of normal, even if there is a concomitant deficiency of body iron.

#### Body Iron Stores

In the absence of external hemorrhage, infectious diseases do not cause detectable changes in the total body content of iron. The infection-induced redistribution of iron within the body leads to an increase in cellular storage forms. Stored iron can easily be detected and visualized by performing iron stains on marrow preparations or liver biopsies. Alternatively, plasma ferritin values can now be measured. Since circulating ferritin in plasma reflects the total quantities of iron present in cellular storage sites, a measurement of plasma ferritin will yield important

diagnostic information about the adequacy of body iron nutrition. Plasma ferritin values will be normal or somewhat higher than normal during an infectious illness despite the concomitantly low plasma iron values.

In the presence of true iron deficiency, iron stores cannot be visualized on direct examination, and plasma ferritin values will be extremely low.

#### Iron Therapy

Table 1 categorizes the changes in various clinical laboratory findings that are important for establishing the correct assessment of the status of body iron nutrition, and thus for selecting the most appropriate course of therapy.

The hypoferrremia of acute infectious disease reflects a purposeful host defensive measure which serves to deny iron to invading microorganisms by increasing the concentration of unsaturated transferrin in plasma. Accordingly, the administration of iron is neither indicated nor warranted. Similarly, if anemia develops during a chronic infection, the most appropriate approach is to diagnose and treat the infection. Once the infection is cured, the anemia should correct itself spontaneously, without the need for a therapeutic intervention with iron.

Therapy of a patient with a true, isolated, deficiency of iron is equally clear-cut. Iron is needed and it should be given.

The very high concentrations of unsaturated plasma transferrin will continue to serve their protective role while the iron deficit is being corrected.

A potential problem in nutritional therapy may occur when iron deficiency coexists with one of protein. The patient faces a situation of double jeopardy; on the one hand, the low concentration of plasma transferrin due to protein malnutrition negates one important host defensive measure, while on the other hand, the iron deficit impairs a number of still more important defensive measures which are based upon lymphocyte and phagocytic cell functions. In such situations, the amount of circulating unsaturated transferrin available to bind iron in plasma can be a key factor when making decisions about therapy. As long as a sizeable portion of transferrin remains unsaturated, the protection it provides will be maintained. Adequate protein nutrition is of primary importance for host defensive mechanisms and iron is a close second. If the iron binding capacity of plasma is very low, protein repletion should take precedence, and oral iron therapy should be delayed or used with extreme caution while insuring that the iron-binding capacity of plasma does not begin to approach a point of near saturation. Parenteral iron administration could be especially dangerous in this regard. Possible latent or concomitant infections should be searched out, diagnosed, and treated at the onset of nutritional therapy, and a



careful watch should then be kept for infections that might emerge or develop during the course of nutritional repletion.

## References

1. Beisel WR: Trace elements in infectious processes. *Med Clin North Am* 60:831-849, 1976.
2. Weinberg ED: Iron and susceptibility to infectious disease. *Science* 184:952-956, 1974.
3. Rogers HJ: Bacterial iron metabolism and host resistance. In Schlessinger D, ed, *Microbiology -- 1974*, p 289-298, Washington, American Society for Microbiology, 1975.
4. Kaplan SS, Basford RE: Exogenous iron and impairment of intraleukocytic bacterial killing, or the leukocyte tells her story. In Schlessinger D, ed. *Microbiology -- 1979*, p 92-95. Washington, American Society for Microbiology, 1979.
5. Holbein BE: Iron-controlled infection with Neisseria meningitidis in mice. *Infect Immun* 29:886-891, 1980.
6. Sutcliffe MC, Savage AM, Alford RH: Transferrin-dependent growth inhibition of yeast-phase Histoplasma capsulatum by human serum and lymph. *J Infect Dis* 142:209-219, 1980.
7. McFarlane H, Reddy S, Adcock KJ, et al: Immunity, transferrin, and survival in kwashiorkor. *Br Med J* 4:268-270, 1970.
8. Murray, MJ, Murray AB, Murray MB, et al: The adverse effect of iron repletion on the course of certain infections. *Br Med J* 2:1113-1115, 1978.
9. Beisel WR, Edelman R, Knauss K, et al: Single nutrient effects on immunological functions. *JAMA* (In press, 1980).

10. Cartwright GE, Wintrobe MM: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXIX. The anemia of infection. Studies on the iron-binding capacity of serum. J Clin Invest 28: 86-98, 1949.

Legends

Figure 1. Sequential changes in mean plasma iron values during experimentally induced tularemia and typhoid fever (1) in relationship to the day of exposure. Arrows depict the period of fever. The horizontal dashed line indicates the preexposure mean value of all subjects.

Table 1

	Infection	Iron Deficiency	Generalized Malnutrition
Plasma iron	Low	Low	Generally low
Plasma transferrin (Total iron binding capacity)	Normal or minimally low	High, up to twice normal	Low. About half of normal
Plasma ferritin	Normal or slightly high	Low	Generally low
Marrow and liver iron stores	Present	Absent	Low to absent

